UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)(KMW)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT GEORGE E. JOHNSON, Ph.D.

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TABLE OF CONTENTS

Page No.

I. PRELIMINARY STATEMENT……..…..1

II. APPLICABLE LAW: THE *DAUBERT* STANDARD…….5

A. Rule 702 of the Federal Rules of Evidence and *Daubert v. Merrell Dow Pharm., Inc.*, 509 US 579 (1993)……..5

.

B. An expert's scientific methodology must be accepted and reliable……..6

C. An expert's opinions are suspect if they rely on his own studies published after being retained for litigation purposes……...8

III. ARGUMENT……9

An expert's methodology must be accepted in the scientific community and Supported by science-based data and analysis……..9

A. The benchmark dose methodology used by Dr. Johnson to calculate Permitted Daily Exposure (PDE) limits for NDMA and NDEA is not used for Class 1 genotoxic mutagens in the wider scientific community……..…9

B. The *Peto (1991)* study supports that NDMA and NDEA are no threshold genotoxic carcinogens which undercuts Dr. Johnson's use of the benchmark dose approach……..…..…..…..…11

C. Dr. Johnson's opinions do not grow naturally and directly out of research independent of this litigation…….……12

D. Dr. Johnson uses evolving, theoretical and conceptual assumptions for his analysis and opinions, which are not reliable and do not constitute "good grounds"……13

E. The established drug regulatory agencies use the TD50 linear extrapolation method and they all agree on the acceptable limits for NDMA/NDEA in drug products…….……17

F. Dr. Johnson is presently undertaking research for the EMA which indicates that his BMD method is not accepted for NDMA and NDEA……..……18

G. An expert cannot "cherry-pick" data in their analysis and disregard important, material data……....21

H. The conclusion that the human DNA repair mechanisms will completely eliminate mutations below PDE is unsupported by scientific evidence……..…..25

I. Dr. Johnson failed to analyze the Dietary and Occupational studies……...…....27

CONCLUSION……30

TABLE OF AUTHORITIES

Cases Page No.

Daubert v. Merrell Dow Pharm, Inc., 509 US 579 (1993)……...5

Daubert v. Merrell Dow Pharmaceuticals (Daubert II), 43 F.3d 1311 (9th Cir., 1995)…….……9

Elcock v. Kmart Corp., 233 F.3d 734, 746 (3d Cir. 2000)…….....7

General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L. Ed. 2d 508 (1997)…...7,8,25

Heller v. Shaw Indus., Inc., 167 F.3d 146, 152 (3d Cir. 1999)…….……..7

In re Human Tissue, 582 F. Supp. 2d 644 (D.N.J, 2008)…….…….……..7

In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig., 509 F. Supp 3d 116 (D.N.J.,2020)……..…….6,7

In re Mirena IUD Levonorgestrel-Related Prods. Liab. Litig., 341 F. Supp. 3d 213 (S.D.N.Y., 2018)……...…….21

In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717 (3d Cir. 1994)…….……5,6,7,29

In re Rezulin Prods. Liab. Litig., 309 F. Supp. 531; 2016 WL 3854534 (S.D.N.Y., 2004) ……..…...21,30

In re Tylenol (Acetaminophen) Mktg., 2016 US Dist. LEXIS 92334; 2016 WL 3854534 (E.D. Pa., 2016)……..…8

In re Zicam Cold Remedy Mktg., Sales, Practices & Prods. Liab. Litig, 2011 US Dist. LEXIS 20356; 2011 WL 798898 (Arizona District Court, 2011)…….8, 25

In re: Zoloft (Sertraline Hydrochloride) Products Liability Litigation, 858 F.3d 787 (3rd Cir. 2017)……...6,7,19

Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999)……..…7

Koninklijke Philips N.V. v. Zoll Lifecor Corp., 2017 US Dist. LEXIS 116337 (W.D. PA, 2017)…….9

Magistrini v. One Hour Martinizing Dry Cleaning, 180 F.Supp.2d 584, 594 (D.N.J.2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003)…….……7, 29

Metabolife Intl., v. Wornick, 264 F. 3d 832 (9th Cir., 2001)……..……9

Oddi v. Ford Motor Co., 234 F.3d 136, 144 (3d Circ. 2000)……..……5

Sakolsky v. Genie Industries, 2021 U.S. Dist. LEXIS 155821; 2021 WL 3661398 (D.N.J., 2021……...……..…..25

Soldo v. Sandoz, 244 F. Supp. 2d 434 (W.D. Pa., 2003)……..……9, 12,13

United States v. Lang, 717 Fed Appx 523 at p. 536. (6th Cir., 2017)……..21

Rules

Fed. R. Evid. 702……..…5,21

I. PRELIMINARY STATEMENT

Plaintiffs bring this motion under *Daubert* to preclude the defense expert toxicologist, George E. Johnson, Ph.D., from offering the opinions contained in his Expert Report on behalf of all defendants at the trial of this matter. Dr. Johnson's Expert Report has been offered by defendants in an attempt to dispute general causation as to whether the genotoxic carcinogens, NDMA and NDEA, found in the common blood pressure medication, Valsartan, resulted in an increased risk of and caused cancer in the patients who took the contaminated Valsartan containing products. Notably, Dr. Johnson's opinion conflicts with the scientific consensus that NDMA and NDEA are recognized as "…two of the most potent mutagenic carcinogens known"[1] which have been classified as Class 1 known mutagenic carcinogens that must be controlled at or below their compound specific acceptable limit.[2]

Dr. Johnson is a genetic toxicologist with a Ph.D.[3] He is not an expert in epidemiology.[4] He is not a medical doctor, chemist, or an expert in pharmaceutical manufacturing.[5] The ultimate conclusion by Dr. Johnson that the amount of NDMA and NDEA in the Valsartan containing drugs poses no risk of cancer to plaintiffs is not scientifically sound since the actual tested levels of contamination in these drugs (which he disregarded) are magnitudes higher in many instances than the Permitted Daily Exposure levels stated in his report.[6]

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[1] Exhibit A-EMA Assessment Report, Angiotensin II Receptor Antagonists, Feb. 2019, p. 37
[2] Exhibit E- ICH M7(R1) FDA Guidance for Industry: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (March 2018), pp. 5, 10-11
[3] Exhibit B-Johnson deposition transcript Day 1, p. 89, 93
[4] Exhibit B-Johnson deposition Day 1, p. 125
[5] Exhibit B-Johnson deposition Day 1, pp. 89, 275
[6] Exhibit C-Johnson Expert Report, p. 58

Dr. Johnson uses a benchmark dose (BMD) methodology to establish his own version of acceptable intake levels – which he refers to as Permitted Daily Exposure (PDE) levels - for NDMA and NDEA. This approach, other than also looking to animal study data, is qualitatively different from the generally accepted TD50 linear extrapolation methodology used by the FDA (United States), EMA (Europe), Health Canada (Canada), PMDA (Japan), Therapeutic Goods Administration (Australia) and other regulatory bodies to determine the acceptable daily intake for NDMA and NDEA. These regulatory bodies use linear extrapolation methodology and have established acceptable daily intake levels of **96 nanograms per day for NDMA** and **26.5 nanograms per day for NDEA.**[7] Dr. Johnson's benchmark dose (BMD) approach is materially different from the approach applied by the FDA and the other regulatory authorities.

The FDA's acceptable intake (AI) limits derive from the ICH M7(R1) Guidance for Industry.[8] This is considered appropriate to derive an acceptable daily intake for M7 Class 1 impurities (known mutagenic carcinogens) with no established threshold mechanism.[9] For NDMA and NDEA, a compound-specific AI can be calculated based on rodent carcinogenicity potency data such as TD50 values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2) identified in the scientific literature. In the case of NDMA and NDEA, the primary public literature relied on is the Peto[10] rat study. The Gold TD50 value for

[7] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, Table 1, p. 10

[8] Exhibit E- ICH M7(R1) FDA Guidance for Industry: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (March 2018)

[9] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, Appendix B

[10] Exhibit F- Peto (1991) *Effects on 4080 Rats of Chronic Ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: A Detailed Dose Response Study* Cancer Research, 51: 6452–6469

NDMA is 0.0956 and the Gold TD50 value for NDEA is 0.0265.[11] The FDA and other regulatory bodies use a linear extrapolation to a probability of 1 in 100,000 which is the accepted lifetime risk level used to establish a safe intake level.[12]

In its *FDA Control of Nitrosamine Impurities in Drugs* published in February 2021, the FDA emphasizes that nitrosamine compounds are potent genotoxic agents which should be controlled at or below a level such that there would be a negligible human cancer risk associated with the exposure.[13] In Appendix B, the FDA states that "linear extrapolation from a TD50 value is considered appropriate to derive an AI for M7 Class 1 impurities (known mutagenic carcinogens) with **no established threshold mechanism**." Then the FDA provides a summary of the acceptable intake (AI) calculation for NDMA as an example of this.[14] The FDA value for NDMA is 0.0959 mg/kg/day (rat, based on Peto et al.).[15] This 96 nanogram value is the maximum allowed by the FDA in a drug taken once per day. Of note, this maximum value is <u>not adjusted</u> by the FDA based upon a patient's weight.

Dr. Johnson's application of his proposed PDE methodology for NDMA and NDEA is not supported by any authority in the field of toxicology and risk assessment. The PDE methodology conflicts with the methodology that is **generally accepted** to determine safe intake

[11] Exhibit G-Lhasa TD50 Carcinogenicity Database Summary Reports for NDMA and NDEA
[12] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, Appendix B
[13] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, p.5
[14] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, Appendix B[15] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, p. 10; Exhibit G-Carcinogenicity Potency Database for NDMA (CAS 62-75-9)
[15] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, p. 10; Exhibit G-Carcinogenicity Potency Database for NDMA (CAS 62-75-9)

levels **of NDMA and NDEA in drugs**. In promoting this approach, Dr. Johnson ignores the guidance by the FDA and EMA that known mutagenic carcinogens such as NDMA and NDEA are defined as "Class 1" which should be controlled at or below the compound specific acceptable limits calculated based on carcinogenic potency and linear extrapolation.[16]

The acceptable daily intake levels Dr. Johnson suggests for NDMA are on the order **of 64 to 220 times higher** than those permitted by the FDA, EMA, or the other regulatory bodies. Similarly, the acceptable daily intake levels Dr. Johnson suggests for NDEA are on the order of **83 to 347 times higher** than those permitted by the FDA. It is thus not surprising that the manufacturers of the contaminated valsartan have proffered Dr. Johnson's construct. Significantly, the specific BMD methodology he applied is only supported by his own 2021 "study."[17]

Underlying the overall conflict with accepted methodology, Dr. Johnson's report lacks scientific rigor and utilizes data selected to support his *a priori* opinions. He chose to use only very limited FDA test results involving data from a few lots,[18] and chose not to consider the extensive manufacturer test results showing higher levels of contamination of NDMA/NDEA. This baseline methodological failure undermines his ultimate opinions that there is no increased risk of cancer for those who took contaminated valsartan, and that contaminated valsartan cannot cause cancer.

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[16]Exhibit E- M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, Guidance for Industry, U.S. Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2018

[17] Exhibit H-Johnson, et. al, *Permitted daily exposure limits for noteworthy N-nitrosamines*, May 2021

[18] Exhibit I-U.S. Food and Drug Administration, Laboratory Analysis of valsartan products, 5/2/2019 at https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.

For the reasons set forth herein, plaintiffs request this Court preclude the opinions and conclusions of George E. Johnson, Ph.D. in their entirety.

II. APPLICABLE LAW - THE *DAUBERT* STANDARD

A. Rule 702 of the Federal Rules of Evidence and *Daubert v. Merrell Dow Pharm, Inc.,* 509 US 579 (1993).

Rule 702 of the Federal Rules of Evidence governs the admissibility of expert testimony. The party offering the proposed testimony must satisfy this burden "by a preponderance of proof." *Oddi v. Ford Motor Co.,* 234 F.3d 136, 144 (3d Circ. 2000) (quoting *Daubert,* 509 U.S. at 593 n.10). Rule 702 requires that a witness offered with specialized knowledge must have sufficient expert qualifications and that the "expert must testify to scientific, technical or other specialized knowledge that will assist the trier of fact." Fed. R. Evid. 702; In *re Paoli R.R. Yard PCB Litigation, 35 F.3d 717 (3d Cir. 1994). To do this, the Court must determine that the expert's scientific testimony or evidence is both relevant AND reliable.*

The District Court must act as a "gatekeeper to assure that the scientific methodology upon which the expert opinion is founded is reliable." *In re Paoli,* 35 F.3d at 732. An "expert's opinions must be based on the methods and procedures of science, rather than on subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 742 (3d Cir. 1994)* (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Paoli* at 745. Judges within this Circuit also consider how and when the

methodology is used outside of litigation. *Paoli*, 35 F.3d at 742 (discussing reliability factors under *Daubert* and Third Circuit case law).

In evaluating a proposed expert's reliability, Courts should take the following factors into consideration: (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put. *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig.,* 509 F. Supp. 3d 116, at 132-133 (D.N.J, 2020).

B. An expert's scientific methodology must be accepted and reliable.

The Third Circuit has held that an "expert's methodology and its application must be reviewed for reliability." *In Re: Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d at 792 (3rd Cir. 2017). The Court observed that, "…to the extent that a doctor utilizes standard diagnostic techniques in gathering this information, the more likely we are to find that the doctor's methodology is reliable." *In Re: Zoloft*, 858 F.3d. at 795. Directly relevant to this motion, the "…use of standard techniques bolster the inference of reliability; nonstandard techniques need to be well-explained." *In Re: Zoloft*, 858 F.3d at 795, (quoting *In re Paoli,* 35 F.3d at 758). There, the Third Circuit excluded the opinions of a general causation expert. The Court found the expert failed to consistently apply the scientific methods he professed to utilize, and had deviated from or downplayed certain well-established principles of his field, "so as to support his *a priori* opinion." *In Re: Zoloft*, 858 F.3d at 792.

The "court must ensure that expert testimony reflects accepted standards within the relevant scientific and business communities." *In Re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig., 509 F. Supp 3d 116* at 131. Simply put, "an expert's opinion must be based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation.'" *In re Paoli*, 35 F.3d at 742.

Dr. Johnson uses a technique and analysis that is not used in the scientific community or by regulators, to determine acceptable intake levels of NDMA or NDEA in drugs. "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 594 (D.N.J.2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003).

The Supreme Court has acknowledged that "conclusions and methodology are not entirely distinct from one another." *General Elec. Co. v. Joiner*, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L. Ed. 2d 508 (1997). Thus, it is acceptable for the court to conduct "at least a limited review of the expert's conclusions 'in order to determine whether they could reliably flow from the facts known to the expert and the methodology used.'" *In re Human Tissue*, 582 F. Supp. 2d 644 at 656 (D.N.J., 2008) (quoting *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 152 (3d Cir. 1999)).

The Court in *In re Tylenol (Acetaminophen) Mktg.*, 2016 US Dist. LEXIS 92334; 2016 WL 3854534 (E.D. Pa. 2016)[19] excluded an expert's opinions where the expert used two recognized

[19] Exhibit Z-*In re Tylenol (Acetaminophen) Mktg.*, 2016 U.S. Dist. LEXIS 92334; 2016 WL 3854534 (E.D., Pa., 2016)

methods of pharmacokinetic calculation, otherwise deemed scientifically reliable, but in a non-accepted manner by combining the two methodologies for one analysis. The Court found that use of these separate methodologies together was not an accepted use by the scientific community. This Court found it notable that "no regulatory agency, such as the FDA or NIH, has used, cited or approved this methodology to determine dosing." 2016 US Dist. LEXIS 92334 at *27-*30. This is particularly relevant here.

C. An expert's opinions are suspect if they rely on his own studies published <u>after</u> being retained for litigation purposes.

The "test of reliability" depends on the "soundness of his methodology". If there is "…simply too great an analytical gap between the data and the opinion proffered" a court may preclude that witness's opinions as speculative or *ipse dixit. In re Zicam Cold Remedy Mktg., Sales, Practices & Prods. Liab. Litig,* 2011 US Dist. LEXIS 20356 at *52-53; 2011 WL 798898[20] (D.C. Az., 2011), citing *General Electric v. Joiner,* 522 US 136,146 (1997).

A court must also "determine whether the experts propose to testify about matters growing out of their own research, independent of the litigation, and if not, whether there exists any other objective, verifiable evidence that the testimony is based on scientifically valid principles." *In re Zicam*, id., at *53. A "very significant fact" to be considered is whether the experts are testifying about their own "independent" research or upon research opinions for purposes of testifying in litigation. *Metabolife Intl., v. Wornick*, 264 F. 3d 832, 841 (9th Cir., 2001); *Soldo v. Sandoz Pharms. Corp*. 244 F. Supp. 2d 434 at 527 (W.D.PA. 2003) Dr. Johnson's opinions in this case were formed with industry assistance and are not independent.

[20] Exhibit AA- *In re Zicam Cold Remedy Mktg., Sales, Practices & Prods. Liab. Litig.,* 2011 U.S. Dist. LEXIS 20356; 2011 WL 798898 (D. C. Az., 2011)

The two primary ways to demonstrate the offered evidence satisfies the reliability standard of Fed. R. Evid. 702 are to show, "that an expert's proffered testimony grows out of pre-litigation research or that the expert's research has been subjected to peer review". *Daubert v. Merrell Dow Pharmaceuticals (Daubert II),* 43 F.3d 1311 (9th Cir., 1995) at p. 1317. *Koninklijke Philips N.V. v. Zoll Lifecor Corp*., 2017 US Dist. LEXIS 116337 *13 (W.D. Pa, 2017) [21]. Neither applies to Dr. Johnson's analysis and opinions herein.

III. ARGUMENT

AN EXPERT'S METHODOLOGY MUST BE ACCEPTED IN THE SCIENTIFIC COMMUNITY AND SUPPORTED BY SCIENCE-BASED DATA AND ANALYSIS.

A. The benchmark dose methodology used by Dr. Johnson to calculate permitted daily exposure (PDE) limits for NDMA and NDEA is not used for Class 1 genotoxic mutagens in the wider scientific community.

Dr. Johnson claims the FDA's TD 50 method is overly conservative and fails to account for the human body's DNA repair systems which he alleges can eliminate exposures to nitrosamines up to a certain threshold, **which is left undefined**. [redacted]

[21] Exhibit BB- *Koninklijke Philips N.V. v. Zoll Lifecor Corp*., 2017 U.S. Dist. LEXIS 116337 (W.D. Pa., 2017)
[22] Exhibit B-Johnson deposition Day 1, pp.271-274

A. [redacted]

The FDA established AI (acceptable intake) levels for NDMA and NDEA in drug products as follows: NDMA: 96 ng/day and NDEA: 26.5 ng/day.[24] [redacted]

The FDA's ICH, March 2018, *Guidance for Industry, M7(R1) Assessment* specifically states that Class 1 Impurities (such as NDMA/NDEA) which are "known mutagenic carcinogens" should be controlled "at or below compound-specific acceptable limit.[26] [redacted]

[23] Exhibit B-Johnson deposition Day 1, pp.271
[24] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, p. 10
[25] Exhibit J-Johnson deposition, Day 2 pp. 345-346
[26] Exhibit E-M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, Guidance for Industry, U.S. Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2018, p. 10
[27] Exhibit B-Johnson deposition Day 1, p. 273
[28] Exhibit K-FDA General Advice to pharmaceutical companies making angiotensin II receptor blockers, (ARB) drug product (DP) regarding the presence of one or more toxic impurities in some ARB drugs (i.e., Valsartan)

[redacted]

The FDA is well aware of the benchmark dose (BMD) method, yet the FDA (and EMA) chose not to use it due to the lack of sufficient data and scientific recognition for NDMA and NDEA.[30] As recently as February 2021, the FDA confirmed in its publication entitled Control of Nitrosamine Impurities in Human Drugs that linear extrapolation from a TD50 value is considered appropriate to derive an AI for M7 Class I known mutagenic compounds with no established threshold mechanism like NDMA and NDEA.[31]

B. The *Peto* (1991) study supports that NDMA and NDEA are no threshold genotoxic carcinogens which undercuts Dr. Johnson's use of the benchmark dose approach.

Dr. Johnson relies on the *Peto*, (1991) study[32] when calculating his permissible daily exposures for NDMA and NDEA.[33] [redacted]."[34]

The Peto study establishes NDMA and NDEA elicit a clear dose response and as the levels of these genotoxins increase in the rats over their lifetimes so do the resulting numbers of cancerous

[29] Exhibit B-Johnson deposition Day 1, pp. 273-274
[30] Exhibit L-EMA Assessment Report, 2020, p. 44
[31] Exhibit D-Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA, Center for Drug Evaluation and Research (CDER), February 2021, Appendix B
[32] Exhibit F- Peto (1991) *Effects on 4080 Rats of Chronic Ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: A Detailed Dose Response Study*, Cancer Research 51, 6415-6451 (1991)
[33] Exhibit C-Johnson Expert Report, p. 13
[34] Exhibit B-Johnson deposition Day 1, at pp. 97-98

tumors in the mammals. The Peto study contains a summary of its findings which include the following:

"The linear relationship observed at low dose rates (below 1 ppm) suggests that under these experimental conditions, among rats allowed to live their natural life span, a dose of 1 ppm of NDEA or NDMA in the drinking water will cause about 25% to *develop a liver neoplasm, a dose of 0.1 ppm will cause about 2.5% to do so, and a dose of 0.01 ppm will cause about 0.25% to do so etc.,* ***with no indication of any "threshold."*** [35] (emphasis added).

The Peto study used by Dr. Johnson does not support his theories or his PDE analysis of a safe threshold. In fact, this study stands for the opposite proposition: **NDMA and NDEA have no indication of any threshold.** For a no threshold genotoxic carcinogen, the linear extrapolation method is the appropriate well accepted proven method and only method currently used. Dr. Johnson accepts the Peto data but disregards **Peto's opposite conclusion** of NO "threshold" for NDEA or NDMA. That renders his methodology arbitrary and unreliable. A condition precedent to using the benchmark dose method is the existence of a threshold dose under which there is no risk of cancer and in this case, there is no such evidence. [36]

C. Dr. Johnson's opinions do not grow naturally and directly out of research independent of this litigation.

"Expert opinions generated as a result of litigation have less credibility than opinions generated as the result of academic research or other forms of "pure" research." *Soldo v. Sandoz Pharms. Corp.* 244 F. Supp. 2d 434 at 527 (W.D. PA., 2003)

[redacted]

[35] Exhibit F-Peto (1991) *Effects on 4080 Rats of Chronic Ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: A Detailed Dose Response Study* p. 1
[36] Exhibit C-Johnson Expert Report, p. 14, 55
[37] Exhibit B- Johnson Deposition Day 1, p. 141-143

[redacted] Significantly, the primary research study that Dr. Johnson relies upon for the application of his BMD methodology and PDE level opinions is his own study, *Permitted daily exposure limits for noteworthy N-nitrosamines*, submitted March 1, 2021 and accepted for publication on May 11, 2021.[39],[40] This study is the only cited study that calculates PDEs for NDMA and NDEA using the BMD. This "study" was conducted **AFTER** he was retained by the defendants in this case, was funded by pharmaceutical company Baxter, International, Inc., and is co-authored by 9 individuals who are employed by major pharmaceutical companies with a vested interest in having higher permissible limits of NDMA and NDEA. [41]

Dr. Johnson's proposed testimony does not grow naturally and directly out of research that he has conducted independent of the litigation, and as such, must be more heavily scrutinized. *Soldo v. Sandoz Pharms. Corp.* 244 F. Supp. 2d 434 at 527 (W.D. PA., 2003)

D. Dr. Johnson uses evolving, theoretical and conceptual assumptions for his analysis and opinions, which are not reliable and do not constitute "good grounds."

Dr. Johnson's Expert Report and testimony contains theoretical and conceptual assumptions including "uncertainty factors", which do not demonstrate scientific reliability.

Dr. Johnson, in his expert report, opines that:

> "…through these calculations that I performed and published in peer-reviewed journals, the patients exposed to valsartan drug products with levels of NDMA below 6.2 u/g/day (upper limit 10.7 u/g) (50 kg person) and 12.4 u/g/day (upper limit 21.4 u/g/day) (100 kg person) do not have an increased risk of cancer.[22] These numbers - 6.2 u/g/day (upper

[38] Exhibit B-Johnson Deposition Day 1, p. 144-145
[39] Exhibit H-Johnson, et. al; *Permitted daily exposure limits for noteworthy N-nitramines*, submitted March 1, 2021, and accepted for publication on May 11, 2021
[40] Exhibit C-Johnson Expert Report, p. 60
[41] Exhibit H-Johnson, et.al, *Permitted daily exposure limits for noteworthy N-nitrosamines*, submitted March 1, 2021, and accepted for publication on May 11, 2021

> limit 10.7 u/g) and 12.4 u/g/day (upper limit 21.4 u/g/day) represent the Permitted Daily Exposure (PDE) of NDMA in a 50 kg patient and 100 kg patient, respectively. Additionally, patients exposed to NDEA below 2.2 u/g/day (upper limit 4.6) (50 kg person) or 4.4 u/g/day (100 kg person) do not have an increased risk of cancer."[42]

Footnote 22 in the above quote from Dr. Johnson's Report uses as authority his own study, Johnson, GE, et.al, *Permitted daily exposure limits for noteworthy N-nitrosamines*, Environmental and Molecular Mutagenesis 62:293-305 (published May 11, 2021). [43] The Court will note that limits found to be acceptable by Dr. Johnson in his report are the same as in his 2021 study for a 50 kg patient, but Johnson did not calculate limits for a 100 kg patient in the 2021 study. This is a methodologically unacceptable approach stealthily introduced under the umbrella of his single article but this theory was only offered in his expert report – not in the article. The FDA has cited the Acceptable Intake (AI) for NDMA at 96 ng and 26.5 ng for NDEA regardless of a person's weight. Adjusting the daily allowable limits of a genotoxic carcinogen by patient's weight is not accepted methodology as evidenced by the FDA which ONLY uses 50 kg human body weight in its calculation.[44] The FDAs above AI is applicable to ALL humans regardless of size.[45]

[redacted]

[42] Exhibit C- Johnson Expert Report, pp. 13-14
[43] Exhibit H-Johnson, GE, et.al, *Permitted daily exposure limits for noteworthy N-nitrosamines*, Environmental and Molecular Mutagenesis 62:293-305 (published May 11, 2021).
[44] Exhibit E-M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk; FDA Guidance for Industry; 2018, p. 37
[45] Exhibit D-FDA, Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, February 2021, pp. 10, 22 and Appendix B

[redacted] (emphasis added).

[redacted] This is evidence that his calculation methods and the data they are based on are not presently widely accepted. **No other studies** in his Expert Report are cited for authority to calculate NDMA/NDEA permissible daily exposures in this manner. There has been no testing or replication of his methodology here for NDMA or NDEA by anyone other than himself.

[redacted], as his "co-authors" included Krista Dobo (listed as with Pfizer), Jim Harvey, Julia Kenny and Anthony Lynch (all listed as being with GSK-GlaxoSmithKline), Sheroy Minocherhomji (listed as being with Amgen), John Nicolette (listed as being with AbbVie), Veronique Thybaud (Sanofi) and Andreas Zeller (Hoffman-LaRoche) who work for the pharmaceutical industry, and funding for this study was by healthcare company Baxter International, Inc.[42,48] [redacted]

[46] Exhibit B-Johnson deposition Day 1, p. 218
[47] Exhibit H-Johnson et al, *Permitted daily exposure limits for noteworthy N-nitrosamines, Environmental and Molecular Mutagens (2021)*
[48] Exhibit B-Johnson deposition Day 1, pp. 218-223
[49] Exhibit B-Johnson deposition Day 1, p. 220-221

[redacted] (emphasis added).

In his report, Dr. Johnson also discusses a theoretical conclusion that endogenous sources of NDMA can be measured in humans sufficiently to opine on their control (or not) by human DNA repair systems. In fact, the table used by Dr. Johnson in his report to demonstrate that "endogenous damage" is not fully considered with the linear approach cited at Figure 6 [52]

[50] Exhibit B-Johnson deposition Day 1, pp. 219-223
[51] Exhibit B-Johnson deposition Day 1, pp. 191-192
[52] Exhibit C-Johnson Expert Report, pp. 32-33

involves "**theoretical dose-response curves**". He only cites to his own study in footnote 70 for support at p. 33 of his report, which has not been scientifically replicated or tested. "Theoretical" data is not reliable or accepted data for his opinions.

E. The established drug regulatory agencies use the TD50 linear extrapolation method and they all agree on the acceptable limits for NDMA/NDEA in drug products.

The regulatory agencies do not agree nor adopt Dr. Johnson's results or analysis. For example, the FDA,[53] EMA,[54] Health Canada,[55] Therapeutic Goods Administration (Australia)[56] and PMDA (Japan)[57] have all determined that the acceptable daily intakes for NDMA and NDEA are as follows: NDMA = 96 nanograms and NDEA = 26.5 nanograms, as opposed to Dr. Johnson's limits.

REGULATORY AGENCY	**NDMA**	**NDEA**
FDA	96 nanograms	26.5 nanograms
EMA	96 nanograms	26.5 nanograms
HEALTH CANADA	96 nanograms	26.5 nanograms
THERAPEUTIC GOODS ADMINISTRATION (AUSTRALIA)	96 nanograms	26.5 nanograms
PMDA (JAPAN)	96 nanograms	26.5 nanograms
DR. JOHNSON APPROACH	6,200-10,700 nanograms (50 kg) 12,400-21,400 nanograms (100 kg)	2,200-4,600 nanograms (50 kg) 4,400-9,200 nanograms (100kg)

[53] Exhibit D-FDA – Control of Nitrosamine Impurities, Guidance for Industry (2021)
[54] Exhibit L-EMA-Nitrosamine Assessment Report (2020), using linear extrapolation TD50
[55] Exhibit M-Health Canada – Q&A on nitrosamine impurities (2020), using linear extrapolation TD50
[56] Exhibit N-TGA (Australia) – nitroso compounds in 'sartan' medicines (2019)
[57] Exhibit O-PMDA (Japan) – Control of Nitrosamine Impurities in sartan drugs (2021)

As can be seen, Dr. Johnson's calculated permissible levels are vastly out of line with those of the authoritative agencies that have undertaken this analysis.[58]

F. Dr. Johnson is presently undertaking research for the EMA which indicates that his BMD method is not accepted for NDMA and NDEA.

[redacted] (emphasis added)

This testimony may demonstrate qualification but does not change the fact that the proposed method is not accepted. As such, Dr. Johnson's entire BMD analysis for NDMA and NDEA is investigational with no other scientific backup.

Even though the EMA **chose NOT to use** the BMD approach because it is not an accepted methodology to set acceptable daily intake for Class 1 mutagenic carcinogens like NDMA and NDEA, the EMA did perform an illustrative Benchmark Dose calculation ($BMDL_{10}$) in its February 14, 2019 report.[60] In this EMA *Assessment*, they calculated a benchmark dose approach AI for NDMA to be **145 nanograms/day (0.145 micrograms/day) for the lower**

[58] Exhibit C-Johnson Expert Report, pp.14-15
[59] Exhibit J- Johnson deposition Day 2, pp. 348-349
[60] Exhibit A-EMA Assessment Report for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group, February 2019

range and 215 ng/day (0.215 micrograms/day) for the upper range. [61] Notably even when using the BMD approach, the EMA then **used linear extrapolation** to arrive at these limits which are slightly higher than the 96 nanogram per day arrived at by the FDA and other regulatory bodies as acknowledged by Johnson.[62] In his BMD analysis, Dr. Johnson omitted linear extrapolation so even his application of the unaccepted BMD methodology is not in line with any accepted or even theoretical alternative. Dr. Johnson's testimony should be excluded because both his method and application are unreliable. See *In Re: Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 792 (3rd Cir. 2017) ("**both an expert's methodology and the application of that methodology must be reviewed for reliability)**, emphasis added.

$BMDL_{10}$ is not a recognized method for Class 1 mutagens. Dr. Johnson disregards the guidance by the FDA and EMA that known mutagenic carcinogens such as NDMA and NDEA are defined as "Class 1" which should be controlled at or below the compound specific acceptable limits calculated based on carcinogenic potency **and** linear extrapolation.[63] All of these factors clearly illustrate how Dr. Johnson's method of calculation is not generally accepted or reliable."

Even Dr. Johnson's ongoing research activities demonstrate that his entire BMD analysis for NDMA/NDEA is investigational. [redacted]

[redacted] Exhibit A-EMA Assessment Report for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group, February 2019, see, table p. 24, p.23

[62] Exhibit J-Johnson deposition Day 2, pp. 371-377

[63] Exhibit E-M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, Guidance for Industry, U.S. Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2018; ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, EMA, August 25, 2015, February 2018

Dr. Johnson's research is subject to bias due to his close working partnerships with major pharmaceutical companies such as GSK, who are funding and approving his research into issues in this litigation. These companies have a vested interest in establishing higher levels of acceptable intake so they can exceed the limits set by the FDA, EMA and others and sell more product. While this goes to the weight and credibility, it also speaks to whether his research is independent and reliable. Proposed research into the mechanisms of these agents is indicative

[64] Exhibit J-Johnson deposition Day 2, pp.358-359
[65] Exhibit C- Johnson Expert Report, pp. 6-7

that the dose-response for mutation of NDMA and the MGMT repair capabilities still need to be quantified.

G. An expert cannot "cherry pick" data in their analysis and disregard important, material data.

Rule 702 of the Federal Rules of Evidence requires that the factual basis of an expert's opinion must be "sufficient." An expert cannot "…cherry pick" only favorable data, which is considered to be as bad as omitting the unfavorable data or making up the data". *United States v. Lang,* 717 Fed Appx 523 536. (6th Cir., 2017). An expert witness is not permitted to "pick and choose" from scientific evidence or ignore evidence that is highly relevant to the opinions being offered and is a basis to exclude that expert's testimony. *In re Mirena IUD Levonorgestrel-Related Prods. Liab. Litig*., 341 F. Supp. 3d 213 (S.D.N.Y., 20180 at p. 241; *In re Rezulin Prods. Liab. Litig*., 309 F. Supp. 531 (S.D.N.Y., 2004) at p. 563. The only levels of contamination analyzed by Dr. Johnson are the very limited lots tested by the FDA.[65] The FDA only tested a small sampling of lots from each manufacturer (1-6 lots tested) when there were actually thousands of lots of valsartan containing drugs manufactured and tested.[66]

The NDMA/NDEA levels detected by the manufacturers' internal testing provide the greatest wealth of data for levels of contamination over the wide range of products by different manufacturers. [redacted] [67] Dr. Johnson did not even use the manufacturers' test data levels of contamination to run a comparison analysis. He

[65]Exhibit C- Johnson Expert Report, pp. 6-7
[66] Exhibit I- FDA *Laboratory Analysis of Valsartan Products, 5/2/2019*, https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products
[67] Exhibit B-Johnson deposition Day 1, p. 258

had access to the manufacturers' data but decided [redacted]

There is no satisfactory explanation as to why only the limited reported FDA test results were used by Dr. Johnson, to the exclusion of far more robust data produced by the defendant manufacturers who hired him. [redacted] stating "[redacted][70] [redacted]

For example, the ZHP/Solco test results itemize the hundreds of Valsartan lots tested. The ZHP/Solco and Torrent testing results do not accord with Dr. Johnson's description of only "Trace Levels of NDMA and NDEA in Valsartan" without defining trace. Apparently, over [redacted] of NDMA is "trace" in Dr. Johnson's world.[72] The FDA's limited test data from a very few lots are not representative of the levels reported [redacted], [74], [75] The NDMA results far exceed those used by Dr. Johnson via the very limited FDA sampling.[76] [redacted]

[68] Exhibit B-Johnson deposition Day 1, p. 252
[69] Exhibit B-Johnson deposition Day 1, p. 251
[70] Exhibits B and J-Johnson deposition, p. 253 (Day 1), p. 381 (Day 2)
[71] Exhibits B and J-Johnson deposition, p. 253 (Day 1), p. 381 (Day 2)
[72] Exhibit C-Johnson Expert Report, p. 58
[73] Exhibit P-Torrent Valsartan NDMA test results; TORRENT-MDL2875-00366172 and for NDEA: TORRENT-MDL2875-00133890
[74] Exhibit Q-ZHP/Solco test results, SOLCO00028261
[75] Exhibit C-Johnson Expert Report, pp. 6-7
[76] Exhibit Q-ZHP/Solco test results, SOLCO00028261

[redacted] To convert the [redacted] found in the API to nanograms in a tablet, one multiplies the ppm by the valsartan dose in the tablet. [redacted]

The high value used by Dr. Johnson to support his opinion that there is no evidence that NDMA or NDEA in valsartan would cause cancer in humans was only 20,190 nanograms, which is the value reported by the FDA. In fact, Dr. Johnson incorrectly states in footnote 24 of his report "the greatest amount of NDMA found in any single batch of valsartan was 20.19 micrograms/tablet." [redacted] The highest NDEA level reported by the FDA was 1,310 nanograms.[81] [redacted] The FDA

[77] Exhibit J-Johnson Deposition, Day 2, p 374
[78] Exhibit C- Johnson Expert Report, pp. 14-15
[79] Exhibit P-Torrent Valsartan NDMA test results; TORRENT-MDL2875-00366172 and for NDEA: TORRENT-MDL2875-00133890
[80] Exhibit P- TORRENT-MDL2875-00133890
[81] Exhibit I- FDA *Laboratory Analysis of Valsartan Products, 5/2/2019*, https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products
[82] Exhibit B-Johnson deposition Day 1, p. 253

published levels clearly were not representative. None of these higher contamination levels [redacted] were noted or analyzed by Dr. Johnson. Dr. Johnson failed to explain why daily doses of NDMA such as [redacted] which far exceeded his PDE levels of 6,200-10,700 nanograms (for 50 kg patient) and 12,400-21,400 nanograms (for 100 kg patient) would not increase the risk of cancer. His failure to consider these significantly higher levels of contamination than the FDA reported values is a fundamental flaw in his analysis.[83] He cites to no authority to support for his statement that "I have seen no evidence of cancer being caused in humans within an order of magnitude higher than the PDE."[84]

Another arbitrary calculation was his use of a "mid-point" on the FDA table of NDMA/NDEA tested levels, which is found in his report's results column. This was not part of the FDA analysis.[85] The use of this mid-point is a statistical device that artificially lowered the highest FDA levels for his analysis. There is no satisfactory explanation for using a mid-point instead of using the data for each range of results, high to low from the FDA and the defendant manufacturers' own test results.

[redacted]

[83] Exhibit C-Johnson Expert Report, pp.14-15 and footnote 24 stating the greatest amount found in any single batch of valsartan was 20.19 micrograms (20,190 nanograms) per tablet.
[84] Exhibit C-Johnson Expert Report, p.15
[85] Exhibit C-Johnson Expert Report, pp. 6-7
[86] Exhibit B-Johnson deposition Day 1, p. 249

[redacted]

Dr. Johnson's decision to cherry-pick a limited data set of test results obtained by the FDA casts serious doubt on his reliability. It creates "too great an analytical gap between the data and the opinions proffered": as per *GE v. Joiner; Id at 146* and becomes *ipse dixit*. See *In re Zicam Cold Remedy Mktg., Sales, Practices & Prods. Liab. Litig,* 2011 US Dist. LEXIS 20356 at *52-53;2011 WL 798898 (Arizona DC, 2011)[88], citing *General Electric v. Joiner,* 522 US 136, 146 (1997).

If Dr. Johnson failed to consider other important data or account for other variables (that an expert in his profession would be expected to do) then he has "failed to exercise the degree of care than an expert would use in his field". This goes directly to the unreliability of Dr. Johnson's methodology and opinions. *Sakolsky v. Genie Indus.,* 2021 US Dist. LEXIS 155821; 2021 WL 3661398 (D.N.J, 2021).[89]

H. The conclusion that the human DNA repair mechanisms will completely eliminate mutations below his PDE is unsupported by scientific evidence.

Dr. Johnson opines that human DNA repair mechanisms will eliminate mutations and repair low levels of specific adducts and mutations.[90] His conclusion that levels of NDMA/NDEA exposure under his "safe levels" are not a human cancer risk is based on unsupported speculation. The studies cited by Dr. Johnson as evidence to support his belief that

[87] Exhibit B-Johnson deposition Day 1, pp. 251-257
[88]Exhibit AA- *In re Zicam Cold Remedy Mktg., Sales, Practices & Prods. Liab. Litig,* 2011 US Dist. LEXIS 20356 at *52-53;2011 WL 798898 (Arizona DC, 2011)
[89]Exhibit CC- *Sakolsky v. Genie Indus*., 2021 U.S. Dist. LEXIS 155821; 2021 WL 3661398 (D.N.J., 2021)
[90] Exhibit C-Johnson Expert Report, p. 29, 26

everyone's DNA repair system will eradicate mutations caused by these specific agents are insufficient to support this bold claim for potent Class 1 mutagens.

The Kaina Chinese hamster cell study, cited in his Expert Report on p. 26 does not stand for the conclusion that our DNA repair mechanisms will remove **all** mutagenic activity by NDMA/NDEA at the PDE cited by Dr. Johnson. [91] The above Kaina study did not even analyze NDMA/NDEA, but rather other nitrosamines.

It is one thing to represent that our human DNA repair systems provide some protection against genotoxic mutations, but quite another to propose a wholesale conclusion that our DNA repair system will eliminate ALL risk of NDMA/NDEA genotoxic effects in everyone exposed. This *ipse dixit* that our DNA repair mechanisms provide a stated and specific level of protection in everyone to the same extent for the PDEs that he calculated is without good scientific grounds and data, and should not be admitted.

Similarly, the other Kaina study cited in his Expert Report[92] (which also did not involve NDMA/NDEA) discussed one of the DNA repair mechanisms for MGMT expression, which protects against some mutations. This Kaina study states that "The protective effects were dependent on the level of MGMT expression, the agent used for alkylation and cell cycle progression."[75] Dr. Johnson provides no scientific data or support to demonstrate the levels of MGMT expression (DNA repair) in persons exposed to NDMA and/or NDEA in valsartan containing drugs are uniform, or at what level they operate in humans of various ages, health,

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[91] Exhibit R-Kaina, et. al, *Transfection and expression of human 06-methylguanine-DNA methyltransferase (MGMT) cDNA in Chinese hamster cells; the role of MGMT in protection against the genotoxic effects of alkylating agents* (1991)

[92]Exhibit S- Kaina, et. al, *Contribution of 06-alkylguanine and N-alkylpurines to the formation of sister chromatid exchanges, chromosomal aberrations, and gene mutations; new insights gained from studies of genetically engineered mammalian cell lines* (1993), p. 1 and Exhibit C-Johnson Expert Report, p. 26

and conditions. The basis for his conclusion that the DNA repair system in humans will conquer his PDE in everyone exposed does not exist, and even [redacted]

None of the studies cited by Dr. Johnson on p. 32 of his Expert Report deal with NDMA/NDEA but rather other agents, many of which are not even nitrosamines. The genotoxic mutagens in this case are the notorious nitrosamines, NDMA and NDEA, not ethylene glycol, pesticides, ethyl mesylate, arsenic, dusts, and fibers. [94] As such, the data and assumptions used by Dr. Johnson are based on arbitrary and incomplete data.

I. Dr. Johnson failed to analyze the Dietary Studies and Occupational Studies.

Dr. Johnson ignored significant scientific data in forming his opinions, by giving no consideration to the dietary studies (that he agreed showed a statistically increased risk of cancer). This is a significant methodological flaw, carefully selecting which data to use to justify his *a priori* conclusions. [redacted] He disregarded all dietary studies and their lower daily NDMA intake amounts without analysis or comment in his report which adds to the unreliability of his process.

Many dietary studies show daily levels of intake in the range of hundreds of nanograms which result in statistically significant increases in cancer risk. For example, DeStefani, Pobel, LaVecchia, and Larsson gastric cancer studies each had statistically significant findings of increased risks of cancer. The DeStefani study reported daily intakes of NDMA equal of 270 nanograms per day were associated with a statistically significant 262% increased risk of gastric

[93] Exhibit J-Johnson Deposition Day 2, p. 522
[94] Exhibit C-Johnson Expert Report, p. 32
[95] Exhibit J-Johnson deposition Day 2, pp. 425-430

cancer (OR=3.62).[96] Similarly, the Pobel study reported NDMA intakes of 290 nanograms per day were associated with a statistically significant 600% increased risk of gastric cancer (OR=7.0)[97], the Larsson study reported that NDMA intakes of 194 nanograms per day were associated with a statistically significant 96% increase risk of gastric cancer (HR=1.96)[98], and the LaVecchia study reported that NDMA intakes of 190 nanograms per day were associated with a statistically significant 40% increase risk of gastric cancer (OR=1.4)[99]. DeStefani also published a lung cancer study reporting that daily intakes of NDMA of 270 nanograms per day were associated with statistically significant 214% increased risk of lung cancer (OR=3.14).[100]

These are just some examples of human dietary epidemiology studies that found statistically significant increased risks of cancer with increasing exposure to NDMA. Importantly, Dr. Johnson did not factor in or compare the daily intake levels from these or any other dietary studies to the permissible daily exposure (PDE) limits he calculated. He did not provide any analysis or explanation as to why the dietary studies find that daily intakes of NDMA in the 100s of nanograms result in statistically significant increased risks of cancer, but his methodology suggests that NDMA daily intakes of between 10,700 (50 kg patient) to 21,400

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[96] Exhibit T-DeStefani E, Boffetta P, Mendilaharsu M et al. Dietary nitrosamines, heterocyclic amines, and risk of gastric cancer: A case-control study in Uruguay. Nutrition and Cancer (1998), p. 158, 161

[97] Exhibit U-Pobel D, Riboli E, Cornée J et al. Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France. Eur J Epidemiol (1995); pp. 67-69

[98] Exhibit V-Larsson SC, Bergkvist L, Wolk A, Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women. Int J Cancer (2006), pp. 915, 919.

[99] Exhibit W-LaVecchia, et al, Nitrosamine intake and gastric cancer risk. European Journal of Cancer Prevention, Volume 4 (1995), p. 469

[100] Exhibit X- De Stefani E, et al., Dietary nitrosodiemethylamine and the risk of lung cancer: A case-control study from Uruguay. Cancer Epidemiology Biomarkers and Prevention (1996), p.681

(100 kg patient) nanograms are safe.[101] Dr. Johnson makes the statement in his report that he has "seen no evidence of cancer being caused in humans within an order of magnitude higher than the PDE" and cites to no authority for this statement.[102] This further demonstrates his failure to consider this category of relevant evidence as the dietary studies report a statistically significant increased risk of human cancer associated with intake levels less than his PDEs.

Similarly, Dr. Johnson failed to provide any analysis of the occupational NDMA studies such as Hidajat[103] in his report.[104] He did not compare the exposures in that study that resulted in a statistically significant increased risk of esophageal, stomach, liver, pancreatic, lung, bladder, prostrate and blood cancer to the levels that he calculated in his PDE approach.

Whenever there is key scientific research data that is the type of data reasonably relied upon by experts that is disregarded without proper explanation, the Court must determine if the proffered opinions are unreliable as not based on data deemed reliable by other experts. See *In re Paoli,* 35 F. 3d at 748. An expert's failure to comment on the potential weaknesses of the studies upon which an expert relies nor to acceptably explain why he did not accord more weight to other studies that did not align with his conclusions may render the opinion unreliable. *Magistrini*, 180 F. Supp. 2d at 584. In this case, the failure of Dr. Johnson to analyze the daily levels of NDMA intake in the dietary and occupational studies which caused a significant increased risk of cancer and compare them to his PDEs demonstrates a fatal failure to account for

[101] Exhibit J-Johnson deposition Day 2, p. 430
[102] Exhibit C-Johnson Expert Report, p.15
[103] Exhibit Y-Hidajat M, et al., Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up, Occupational and Environmental Medicine (2019), pp. 250, 255-256
[104] Exhibit C - Johnson Expert Report

all categories of relevant evidence which renders the opinion unreliable. See *In re Rezulin Products Liability Litigation,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005).

CONCLUSION

For the foregoing reasons, Dr. George Johnson should be precluded from offering his opinions related to general causation.

Respectfully submitted,

Rosemarie Riddell Bogdan

CERTIFICATE OF SERVICE

I hereby certify that on November 1, 2021, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notifications of such filing to the CM/ECF participants registered to receive service in this MDL.

/s/ Rosemarie Riddell Bogdan
Rosemarie Riddell Bogdan